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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/560,098	MIYAZAKI ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/23/08 and 6/13/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6 and 8-22* is/are pending in the application.

4a) Of the above claim(s) *3,4 and 9-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,8 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/22/08 and 4/23/08* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 3, 4, 6, 8-22 are all the pending claims for this application.

2. Claims 2, 5, and 7 were cancelled and Claims 1, 6, 8, and 22 were amended in the Response to the Notice of Non-Compliance of 6/13/08.

3. Claims 3, 4, 9-21 are withdrawn from examination.

4. Claims 1, 6, 8 and 22 are all the pending claims under examination.

5. Applicants amendments to the claims have necessitated new grounds for objection and rejection. This action is FINAL.

Information Disclosure Statement

6. The U.S. patent reference and the non-patent literature references cited in the IDS' of 1/22/08 and 4/23/08 have been considered and entered. The initialed copies of the 1449 forms are attached.

Withdrawal of Objections

Specification

7. The amendment to the specification to insert the section "Brief Description of the Figures" (on pp. 22-23 of the specification) between the "Brief Summary of the Invention" and "Detailed Description of the Invention" meets and overcomes the objection.

Claim Objections

8. The objection to Claims 5-8 in depending from non-elected claims 3 and 4 is moot for cancelled Claims 5 and 7 and withdrawn for Claims 6 and 8 in view of the amendment of Claim 6 to depend from Claim 1.

9. The objection to Claim 22 for an apparent typographical error “expressions” is moot for the deletion of the phrase containing the misspelling from the claim.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

10. The rejection of Claims 1 and 5-8 as being incomplete for omitting essential steps, such omission amounting to a gap between the steps is moot for cancelled Claims 5 and 7 and withdrawn for Claims 1, 6 and 8 in view of the amendment of Claim 1 to recite what appears to be a different invention, but which nevertheless recites the steps for practicing the method.

11. The rejection of Claims 5-8 in lacking antecedent basis for the limitation "the first and the second H chain” and “the first and the second L chain" in Claim 5 is moot for cancelled claims 5 and 8. Claims 6 and 8 have been amended to depend from Claim 1.

12. The rejection of Claim 7 in lacking antecedent basis for the limitation "the first pairs or the second pairs" is moot for the cancelled claim.

13. The rejection of Claims 7 and 8 for the phrase "the antibody is unlikely to be formed from a combination of just the first pairs or the second pairs" is moot for cancelled Claim 7 and withdrawn for Claim 8 in view of the amendment of the claim to delete the phrase.

14. The rejection of Claims 2, 5-8 and 22 for the recitation "a first pair and a second pair of the antibody" in Claim 2 is moot for the cancelled claim.

15. The rejection of Claim 22 for omitting essential elements (e.g., the vector *encoding* the first H chain and first L chain under the control of a first inducible promoter and the vector encoding the second H chain and second L chain under the control of a second inducible promoter. It is not clear how each vector, each pair of H and L chains and the expression regulator are physically or structurally related) is withdrawn in view of the amendment of the claim to recite the reagents used in the method steps.

Claim Rejections - 35 USC § 103

16. The rejection of Claims 1, 2 and 5-8 under 35 U.S.C. 103(a) as being unpatentable over Carter et al., (J. Immunol. Methods 248:7-15 (2001); cited in the IDS of 4/28/06) in view of Peipp et al., Biochem. Soc. Trans. 30:507-511 (2002); cited in the IDS of 4/28/06) and Shalaby et al., J. Exp. Med. 175:217-225 (1992); cited in the IDS of 4/28/06) is moot for cancelled Claims 2, 5 and 8, and withdrawn for Claims 1, 6 and 8.

Applicants have amended the claims to recite that a bispecific antibody is expressed in the same cell and where the expression of the first light and heavy chain is temporally separated from the expression of the second light and heavy chain, and the light chains of the bi-specific antibody and the heavy chains of the bispecific antibody are different.

Applicants allegations on p. 10 of the Response of 4/23/08 describing how a full length antibody having a knobs-in-holes engineered into the Fc domain is not suitable for expression in bacterial expression systems of Shalaby because Peipp suggests that such antibodies as compared to diabodies or Fab cannot be effectively produced in E. coli is acknowledged.

Rejections Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

17. The rejection of Claims 1, 6, 8 and 22 under 35 U.S.C. 103(a) as being unpatentable over Ridgeway et al., (Protein Eng. 9:617-612 (1996); cited in the IDS of 4/28/06) in view of Peipp et al., (Biochem. Soc. Trans. 30:507-511 (2002); cited in the

IDS of 4/28/06) and Shalaby et al., (J. Exp. Med. 175:217-225 (1992); cited in the IDS of 4/28/06) is maintained.

Note, this 103 rejection is not being applied to element (ii) of amended Claim 22, which as discussed below, is not enabled for an expression vector construct comprising both the first and the second light chain and heavy chain pairs, and is differentially regulated in its expression of the first and the second antibody pairs and which is expressed in the same cell.

The rejection was set forth in the Office Action of 10/23/07 as follows:

"Ridgeway describes a process for producing a bispecific antibody having an Fc region, wherein the H chain and L chain which constitute a first set have a antigen recognition site and the H chain and L chain which constitute a second pair have another antigen recognition site and are expressed simultaneously, and the formation of the first pair and the second pair and the bonding of said first pair and second pair by knobs-in-hole are carried out simultaneously. Ridgeway also describe antibodies produced having antigen recognition sites comprising the H chain which makes up the first pair and the L chain which makes up the second pair. Ridgeway does not disclose expressing the first and second antibodies at different times but Peipp and Shalaby rectify this deficiency.

Peipp and Shalaby are discussed supra.

One skilled in the art would have been motivated at the time of the invention to have made the process for producing a bispecific antibody having an Fc region and been reasonable assured of success based on the disclosures of Ridgeway, Peipp and Shalaby. The method of Ridgeway could readily have been modified by one of skill in the art based on Pipp and Shalaby disclosing that the separate expression of an H chain and L chain which constitute a first pair having a particular antigen recognition site and an H chain and L chain which constitute a second pair having another antigen recognition site, and to bond their respective H chain and L chains in advance, forming a first pair and a second pair having antigen recognition site, and subsequently bonding the first pair and second pair via knob-in-hole, in order to prevent the production of antibodies having antigen recognition sites comprising undesirable sets and to efficiently produce the target bispecific antibody. Further one of skill in the art could introduce an optimum expression regulating factor and carry out the expression of the H chain and L chain which constitute the first pair, and an H chain and L chain which constitute the second pair in separate cells at different times. Because Ridgeway taught the general method for producing bispecific antibodies and Peipp and Shalaby describe different techniques for expressing different antibody pairs from different vectors could be accomplished in E. coli, one of ordinary skill in the art could have readily introduced the vector system of Peipp or Shalaby into the method of Ridgeway and would be reasonably assured that the expressed antibody pairs would have formed a bispecific antibody."

Applicants' allegations on p. 11 of the Response of 4/23/08 have been considered but are not found persuasive. Applicants allege "Indeed, the knobs-in-holes method used by Ridgeway is very similar to that of Carter"; and the rejection over

Ridgeway, Peipp and Shalaby is incorrect for the same reasons the rejection over Carter, Peipp and Shalaby is incorrect.

Response to Arguments

Applicants do not appear to have taken the time to review Ridgeway, or the disclosure relied on by the examiner was overlooked. Ridgeway teaches co-transfection of phagemids encoding the anti-CDR3 L chain and H chain into human embryonic kidney cells, 293S, *together* with a CD4IgG variant encoding phagemid. This is interpreted as the antibody being expressed by the same cell. Mutations were constructed in the CH3 domain of humanized anti-CD3 Ab H chain and in the CD4-IgG, and the CH3/CH3 interface involves 16 residues on each domain. In contrast to chains containing the wild-type CH3, the hybrid was recovered in yields of up to 92% from co-transfections in which the anti-CD3 H chain and CD4-IgG contained the Y407T hole and T366Y knob mutations, respectively. Further because each of the Ab and the CD4-IgG of Ridgeway is expressed on a different phagemid within the same cell, there is no requirement that the proteins would necessarily be expressed at the same time absent a showing by Applicants to the contrary.

Ridgeway states: "This augurs well for the preparation of larger quantities of hybrids using stable cell lines where the relative expression levels of the Ab and CD4-IgG are less readily manipulated than in the transient expression system used here."

Ridgeway states: "The T366Y and Y407T mutations are directly applicable to the construction of bispecific IA, which further expand IA as a class of novel therapeutic. In addition the mutations identified are anticipated to increase the clinical potential of ***Fc-***

containing BsAb by reducing the complexity of the mixture of products obtained from a possible 10 major species down to four or less."

Rideway provides sufficient motivation to use the holes-to-knobs approach in a single cell system to create other antibody fragments such as the bispecific antibodies of the instant claims including the BsF(ab)2 of Shalaby. Shalaby provides methods for expressing a Fab' in a dicistronic format where both the light chain and heavy chain are under the transcriptional control of the phoA promoter. The general skills and technology to modify the expression unit of Ridgway according to the expression units of Shalaby for use in the method of Ridgeway would seemingly have been obvious at the time of the invention especially to produce a full length bispecific antibody within the same cell.

Rideway provides sufficient motivation to use the holes-to-knobs approach in a single cell system to create other antibody fragments such as the bispecific antibodies of Peipp. Peipp teaches "Recombinant bispecific antibodies can be successfully produced in various expression systems (see Table 2 for examples of expressing recombinant bispecific antibodies in CHO cells)"...and "While bacterial expression offers the potential for large yields, difficult refolding procedures may be required to obtain functional proteins. Today, production in Escherichia coli is most commonly used for the diabody format, while short-chain bispecific antibodies are preferentially expressed in mammalian cells. Interesting novel expression systems include yeast or insect cells, as well as transgenic plants or animals [38,39]. For production of clinical-grade material, however, these later systems are less well defined regarding potentially dangerous

contaminants, and furthermore differ substantially from mammalian cells with respect to their glycosylation pattern."

Thus in order to produce abundant yield of heterodimeric, bispecific antibodies which are optimally expressed, dimerize with their corresponding complementary chain and are properly glycosylated, the ordinary artisan would have found more than sufficient motivation to have used the method of Ridgeway as a starting point for expressing heterodimeric antibodies in a single eukaryotic cell using a dicistronic vector or separate vectors encoding the light and heavy chain complementary pairs in order to ensure differentially timed expression for equimolar expression and dimerization of the complementary light and heavy chain in order to avoid mispairing followed by the further pairwise association of the different heavy chains through the knobs-to-holes variation.

New Grounds for Objection

Claim Objections

18. Claims 8 and 22 are objected to for objected to because of the following informalities:

a) Claim 8 is objected to for the semicolon ";" occurring after "Claim 1" which should seemingly recite a comma ",";

b) Claim 22 is objected to for the apparent misspelling in line 5 for "he" which should seemingly recite "the.

Appropriate correction is required.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

19. Claims 1, 6, 8 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of transfecting a eukaryotic cell - with a vector or vectors encoding the light and heavy chain of one pair and a vector or vectors encoding the light and heavy chain of a second pair where each pair is under the control of a different regulatable promoter in order to differentially express each pair and to allow for the pairwise assembly of the expressed pairs through a knobs-to holes mutation introduced into the heavy chain portion of the first and second heavy chain, does not reasonably provide enablement for inducing just any kind of cell to express a first light chain and a first heavy chain at one time and to express a second light chain and a second heavy chain at a different time under just any conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in

the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the Invention/ Skill in the Art

Claims 1, 6, 8 and 22 are interpreted as being drawn to a method for producing an antibody in a cell comprising expressing a first light and heavy chain at one time and expressing a second light and heavy chain at a different time and where the light chains are different and the heavy chains are different (Claim 1), where the antibody is bispecific and the first light and heavy chain recognize one antigen and the second light and heavy chain recognize a second antigen (Claim 6), where the antibody is prepared by using the knobs-into-holes technique (Claim 8), and where the first light and heavy chain expression is under the control of a first expression regulator and the second light and heavy chain expression is under the control of a second expression regulator and each of the expression regulators are different, where (i) the first light and heavy chain and second light and heavy chain are encoded by the same vector or (ii) the first light and heavy chain are encoded by a first vector and the second light and heavy chain are encoded by a second vector (Claim 22).

The relative skill in the art required to practice the invention is a molecular immunologist.

Disclosure of the Specification

Specific examples of methods for expressing the first and second pairs of antibodies at different times include methods that induce the expression of the first and second pairs of antibodies at different times using expression regulators. More specifically, a vector in which expression of a first pair can be induced by a first expression regulator, and a vector in which expression of a second pair is inducible by a second expression regulator, are constructed. The first pair and second pair may be constructed in a single vector, or two or more different vectors. Alternatively, the H chain and L chain may be constructed in a single vector, or two or more different vectors. Next, the obtained vector constructs are introduced into cells, and expression of the first pair is induced by the first expression regulator, and then expression of the second pair is induced by the second expression regulator. In this case, expression of the first pair is preferably turned off before expression of the second pair is induced [0056].

A specific example of the methods for producing antibodies of the present invention is described where “First, the H and L chains on the left arm of an antibody (Left HL) and the H and L chains on the right arm of the antibody (Right HL) are respectively cloned into a tetracycline inducible pcDNA4 vector (Invitrogen) and an ecdysone inducible pIND vector (Invitrogen). All of the expression-regulated plasmids are introduced into the above-mentioned suitable host cells, for example, animal cells such as COS-7 cells. For example, for the first induction tetracycline is added to the medium, and a Left HL molecule is formed in the cells. One to two days after the first induction, the medium is washed away to completely remove the first agent (tetracycline, in this case). Next, the cells are placed in a fresh medium containing an

ecdysone analogue, the agent for the second induction, and the second induction is conducted for two to three days. Consequently, a Right HL molecule is produced and associates with the Left HL molecule already present in the cells, thus forming a complete BsAb form, which is then secreted into the medium" [0065].

The expression regulators are not particularly limited, and any kinds of expression regulators may be used as long as they can regulate expression of H chains and L chains in host cells. For example, expression may be induced in the presence of an expression regulator, and not in its absence; or conversely, expression may be induced in the presence of an expression regulator, and not in its absence. Expression regulators may be chemical compounds such as expression inducing agents, or physical factors such as temperature (heat). Specific examples of expression inducing agents include antibiotics such as tetracycline, hormones such as ecdysone analogues, and enzymes such as Cre (a homologous recombination enzyme which causes recombination). In addition, induced expression of an H chain and/or L chain may be halted by removing the expression inducing agent that functions as an above-mentioned expression regulator. If a physical factor such as temperature (heat) is used as an expression regulator, the induced expression of an H chain and/or L chain can be halted by returning to a temperature that does not permit induction of expression [0057].

Claim 22, element (i) is drawn to expressing both antibody pairs from the same vector, and the specification provides a single statement for expressing both antibody pairs from the same vector. No examples of a poly-cistronic expression vector are

taught or disclosed, and no references citing examples of a poly-cistronic expression vector are cited which meet all the required claim limitations.

A method using any cell with the properties of the instant claims is unpredictable and requires undue experimentation.

In order to obtain a bispecific antibody comprising the heavy and light chain constant domains and using the knobs-to-holes technique required by the instant method, and in order to produce abundant yield of heterodimeric, bispecific antibodies which are optimally expressed and dimerize with their corresponding complementary chain and are properly glycosylated, the ordinary artisan could not have used just any wild-type cell as instantly claimed. This is because according to Peipp (Biochem. Soc. Trans. 30:507-511 (2002); cited in the IDS of 4/28/06) “Recombinant bispecific antibodies can be successfully produced in various expression systems (see Table 2 for examples of expressing recombinant bispecific antibodies in CHO cells)"...and “While bacterial expression offers the potential for large yields, difficult refolding procedures may be required to obtain functional proteins. Today, production in Escherichia coli is most commonly used for the diabody format, while short-chain bispecific antibodies are preferentially expressed in mammalian cells. Interesting novel expression systems include yeast or insect cells, as well as transgenic plants or animals [38,39]. For production of clinical-grade material, however, these later systems are less well defined regarding potentially dangerous contaminants, and furthermore differ substantially from mammalian cells with respect to their glycosylation pattern.” Further, Ridgeway et al., (Protein Eng. 9:617-612 (1996); cited in the IDS of 4/28/06) teach the successful use of

an in vitro eukaryotic cell system to express an Ab/CD4-IgG using the knobs-to-holes technique which is taught as being adaptable to creating bispecific antibodies.

The specification does not nearly suggest that the ordinary artisan could remotely practice the invention using any cell and in the absence any particular reagents as is otherwise required by the instant claims. The ordinary artisan would be required to practice undue trial and error experimentation just to identify any wild-type cell having the ability to differentially express a first light and heavy chain much less a second light and heavy chain within the same cell, and further wherein the antibody is generated using a knobs-into-holes technique when the instant claims which do not specify where within the antibody structure, the knobs-to-holes mutation should be introduced. Thus Applicants have not identified a naturally occurring cell that can be induced under any conditions to express two different antibodies (or antibodies against different antigens) within or by the same cell.

Similarly, the ordinary artisan would be required to perform undue trial and error experimentation to test various different compounds for expression regulating effects on the endogenous promoters for the first light and heavy chain, and different compounds for expression regulating effects on the endogenous promoters for the second light and heavy chain, especially where the compound-inducible expression regulation is required to be performed in the same cell in order for the same wild-type cell to differentially express the different light/heavy chain pairs.

The ordinary artisan would be required to practice undue trial and error experimentation in order to construct a poly-cistronic vector enabled to express in a

different time frame the first antibody pair and then the second antibody pair and all occurring within the same cell, because no guidance is provided in the original specification as filed for the starting materials and/or the generation of any such vector construct.

Applicants could overcome the rejection by introducing amendments into the method claims more particularly describing those steps and reagents which are required to practice the method as supported and enabled by the original disclosure.

Conclusion

20. No claims are allowed.

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

/David J Blanchard/
Primary Examiner, Art Unit 1643